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DRUG DISCRIMINATION USING A CONDITIONED TASTE-AVERSION PARADIGM IN RHESUS MONKEYS

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The development of drug discrimination was assessed in rhesus monkeys using the conditioned taste-aversion paradigm. Monkeys were initially trained to respond under a fixed-ratio 30-response schedule of food-pellet delivery to assess the rate-decreasing effects of alprazolam (0.03 to 3 mg/kg, i.m., 60 min presession). Alprazolam decreased responding at doses greater than 0.1 mg/kg. Discriminative stimulus effects of alprazolam were then assessed by giving 0.03 mg/kg before sessions in which 1.8 mEq/kg lithium chloride was given immediately after the session (alprazolam/lithium session). On intervening days, saline was given before and after the session (saline/saline session). Rates of responding decreased over successive alprazolam/lithium sessions and also during the saline/saline session that immediately followed an alprazolam/lithium session. During subsequent saline/saline sessions, rates of responding returned to levels near baseline rates within two to four sessions. The discriminative stimulus effects of alprazolam were then assessed by giving 0.1 mg/kg before sessions in which 1 mg/kg *d*-amphetamine was given immediately after the session (alprazolam/*d*-amphetamine session). Rates of responding decreased during subsequent alprazolam/*d*-amphetamine sessions in drug-experienced monkeys, but did not decrease during intervening saline/saline sessions. These findings demonstrate that drug stimuli associated with postsession drug injections can rapidly develop control over behavior and suggest that similar methods be explored in the assessment of drug discrimination.

Key words: drug discrimination, conditioned taste aversion, alprazolam, fixed-ratio schedule, lever press, rhesus monkeys

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Drug-discrimination procedures assess the ability of an agent to exert stimulus control by developing contingencies between the presence or absence of that agent and a specific outcome (Overton, 1987). Typically, a discrete response in the presence of a drug is maintained by food presentation, whereas a different response is maintained in the absence of the drug. These procedures provide a powerful approach toward studying the stimulus effects of drugs, but may be laborious to establish (Overton, 1987).

Recently, there have been several reports of the rapid development of drug discrimination using a conditioned taste-aversion paradigm. Typically, water-deprived rats are pretreated with a drug, given access to saccharin-flavored water, and then given an agent known to produce a conditioned taste aversion. The amount of fluid consumed on subsequent drug days is compared with that consumed on days the vehicle is given before and after sessions with saccharin-flavored water. For example, in one series of reports (Mastropaolo, Moskowitz, Dacanay, & Riley, 1986, 1989), rats were injected with phencyclidine (PCP), provided access to a saccharin solution, and then injected with 1.8 mEq/kg lithium chloride (LiCl; PCP/saccharin/LiCl session). On intervening days, the rats were injected with distilled water prior to access to the same saccharin solution and given a distilled water injection immediately afterward. Although the rats initially consumed saccharin after the first injection of PCP, a significant decrease in saccharin consumption developed by the third PCP/saccharin/LiCl session, and almost complete suppression of drinking occurred by the sixth session. Consumption was not suppressed when the vehicle was given prior to access to saccharin. The conditioned taste-aversion paradigm has been used to assess discriminative stimulus effects of several other drugs, including a series of serotonergic agents (Lucki, 1988), naloxone (Kautz, Geter, McBride, & Riley, 1989), and pentobarbital (Riley, Jeffreys, Pournaghash, Titley, & Kufera, 1989). The results suggest that the taste-aversion paradigm can be used to establish drug discrimination rapidly.

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Although taste aversions have typically been assessed by changes in the consumption of food or water, changes in operant responding have also been used to study this effect (Bergman & Glowa, 1986; Glowa & Barrett, 1983; Stolerman & D'Mello, 1978). For example, when responding by squirrel monkeys was maintained under a fixed-ratio (FR) 30 schedule of food pellet presentation, pairing the type of food pellet (banana vs. sucrose) produced under the FR schedule with postsession drug injections decreased responding that produced the drug-paired food pellet (Bergman & Glowa, 1986). Pellets paired with postsession saline injections had no effect on responding. This effect was also rapidly obtained, suggesting that response suppression under operant designs may also be well suited for the study of drug discrimination.

The present study was designed to assess the possibility that response suppression produced by postsession drug administration could be brought under the discriminative control of low doses of alprazolam (ALPZ). To assess this possibility, low doses of ALPZ were given before sessions in which the responding of rhesus monkeys was maintained under a food-presentation schedule. Following these sessions, the monkeys were given an injection of another drug. The result confirmed that the conditioned taste-aversion design can result in a rapid change in behavior. The selective decrease in responding on days when ALPZ was given before the session was consistent with the acquisition of drug-mediated stimulus control.

EXPERIMENT 1

The first experiment assessed the ability of low doses of ALPZ to serve as a discriminative stimulus for postsession administration of LiCl. In order to assess the appropriate dose of ALPZ to be used, it was first necessary to establish a dose–effect function for its rate-decreasing effects. This would allow the assessment of the discriminative effects of ALPZ at doses without direct rate-decreasing effects. Following this, monkeys were given ALPZ before sessions that were followed by LiCl injections.

METHOD

Subjects

Four male adult rhesus monkeys (*Macaca mulatta*), weighing approximately 8 to 9 kg, served as subjects. Two monkeys, 8221 and 59, had extensive prior histories of food-maintained responding and prior exposure to ALPZ. The other two, 512 and 72, were experimentally naive. Between experimental sessions, subjects were housed individually and had continuous access to water. Weights were maintained at 85% of ad libitum weights by restricting access to food (Purina® Monkey Chow) in the home cages.

Apparatus

During experimental sessions, monkeys were seated in one of two Plaslabs Plexiglas chairs (see Glowa, Skolnick, & Paul, 1986). The chair was placed in one of two ventilated, sound-attenuating chambers (Industrial Acoustics, Model AC-5) provided with white noise to mask extraneous sounds. A response lever (BRS/LVE, Model 121-05), modified with a solid Plexiglas paddle, was mounted on the transparent front wall of each chair. Each press on the lever with a minimum downward force of 0.20 N produced an audible click of a relay within the chamber and was recorded as a response. Triplets of blue and red lamps, mounted at eye level behind the front wall, were illuminated to serve as visual stimuli. A food pellet dispenser (BRS/LVE, PDC-050) was mounted on each chair; 1-g sucrose or banana-flavored pellets (Noyes) could be delivered to a tray accessible to the monkey through an opening in the front of the chair. Experimental conditions were controlled through a 64K experimental controller (Palya, 1988) connected to a Macintosh® computer. Cumulative recorders were used to monitor behavior.

Procedure

Naive monkeys were trained to respond by first adapting them to increasing periods in the chair, and then in the chamber, while at the same time decreasing the amount they were fed in the home cage. Magazine training occurred during adaptation to the chair. Initially, the monkeys were shaped to press the lever by placing a pellet behind the front panel, directly over the lever. During the first few days of training, each response in the presence of lighted blue stimuli produced a food pellet. The response requirement was gradually raised to 30 over a period of about a week.

Under the final conditions of the experiment, responding was maintained under an

FR 30 schedule of food presentation. In the presence of the blue lamps, each 30th response produced a food pellet, followed by a 1-s timeout. Stimuli were off during timeout, and responding had no scheduled consequences. If 30 responses did not occur within 60 s, the ratio requirement reset (limited hold, LH 60 s) without a stimulus change. Sessions consisted of 80 FR 30s and, thus, could range in duration from the minimal time required to produce 80 food pellets to 80 min, although the latter never occurred. Experiments were conducted at least 5 days per week.

Dose–Effect Assessment: Experiment 1a

In the first experiment, the 4 monkeys were trained under an FR 30 schedule of banana-pellet presentation. After responding was stable, the effects of ALPZ (0.03 to 3 mg/kg) were determined by administering single doses (in the home cage) 60 min prior to daily sessions on Tuesdays and Fridays. Effects of each dose were determined two or three times in each monkey. Doses were given in a pseudorandom order. Data from Thursdays served as a control.

Drug-Discrimination Assessment: Experiment 1b

Monkeys 72 and 512 were used to assess the efficacy of ALPZ as a discriminative stimulus in the conditioned taste-aversion design. Each monkey was first given a saline injection (in the home cage) 60 min before a session and was then exposed to sucrose pellets by delivering those pellets under the FR 30 schedule in an otherwise typical daily session. Immediately after that session the monkey was given another saline injection (and left in the chamber for 15 min). This exposed the monkeys to both injection procedures and assessed the efficacy of sucrose pellets as a reinforcer. Sucrose pellets were used for the remainder of the experiment. In the next phase of the experiment, 0.03 mg/kg ALPZ was given before certain sessions, and 1.8 mEq/kg LiCl was given immediately after the same session (ALPZ/LiCl). On other days, saline was given before and after the session (saline/saline). The monkeys remained in the chamber for 15 min after either type of postsession injection. The sequence of an ALPZ/LiCl session followed by one or more saline/saline sessions was repeated for seven cycles. ALPZ/LiCl sessions were conducted only if the preceding day's baseline rates of responding exceeded a criterion of 1.0 responses per second.

Drugs

Alprazolam (Upjohn) was dissolved in warmed ethanol (5%) and mixed with propylene glycol (5%) and then saline. Doses were given i.m. in the thigh muscle in a volume of 0.1 mL/kg body weight. Lithium chloride (Sigma) was dissolved in 3 mL 0.9% saline solution and given i.m. in the thigh.

RESULTS

Baseline Performances

Rates and patterns of responding were similar to those seen previously under FR schedules with other species. Generally, each FR began with a brief pause that was followed by a sustained high rate of responding. Experimental conditions and respective control rates of responding across conditions are presented in Table 1.

Dose–Effect Assessment: Experiment 1a

Figure 1 shows that ALPZ decreased FR responding as a function of increasing dose for each animal. The mean rate-decreasing effect was minimal at doses of 0.03 to 0.1 mg/kg, whereas doses of 1 to 3 mg/kg either substantially or completely abolished responding. The lower right frame shows the effects of three successive dose–effect determinations in the 2 naive monkeys. The effects of 0.03 to 1 mg/kg ALPZ diminished with repeated determinations.

Drug-Discrimination Assessment: Experiment 1b

The injection procedure and substitution of sucrose pellets had no effect on responding. Figure 2 shows that when 0.03 mg/kg ALPZ was given 60 min before sessions that were immediately followed by a LiCl injection, responding decreased over those sessions. By the third ALPZ/LiCl session responding decreased from baseline rates, to 25% of control for Monkey 512 and 2% of control for Monkey 72. Responding recovered somewhat during the fourth ALPZ/LiCl session, but then generally remained low over subsequent ALPZ/LiCl sessions. Responding also decreased over saline/saline sessions, (i.e., sessions preceded by and followed by saline injections), generally paralleling the effects seen during ALPZ/LiCl sessions. Figure 2 also shows the mean change

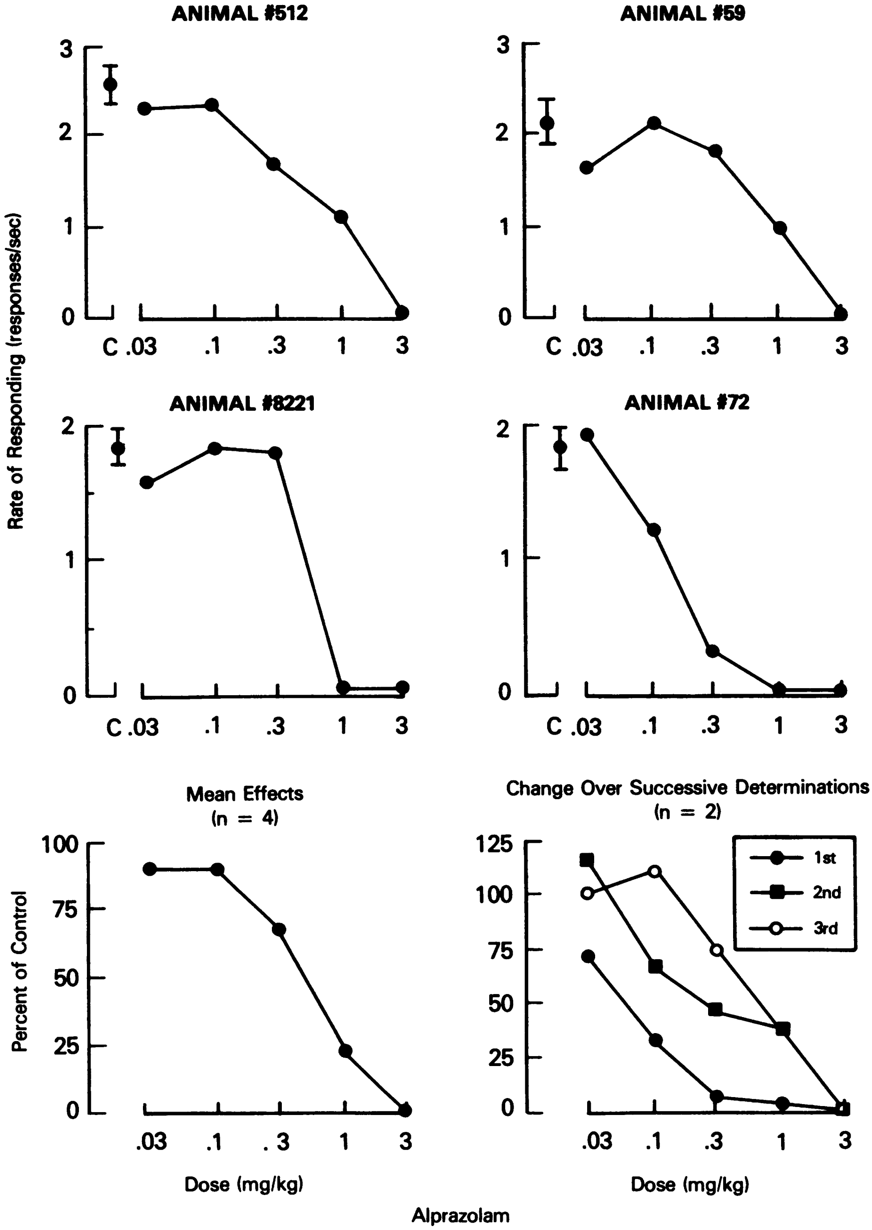

Fig. 1. Individual dose-effect functions for alprazolam (0.03 to 3 mg/kg) on absolute response rate maintained under FR 30 schedules of food presentation, the mean function as a percentage of control for the 4 monkeys studied (lower left), and the mean change in dose effect as a function of repeated (one to three) determinations for Monkey 512 and Monkey 72 (lower right).

in the overall session response rate in successive saline/saline sessions that followed an ALPZ/LiCl session. Although rates of responding decreased on saline/saline days immediately following ALPZ/LiCl days, they generally recovered to criterion levels within one to four saline/saline sessions.

Discussion

ALPZ decreased FR responding in a dose-related manner. Not unexpectedly, some tolerance to these rate-decreasing effects occurred (we have previously seen complete tolerance to large rate-decreasing effects of 3 to 5.6 mg/

kg alprazolam on FR food-maintained responding in rhesus monkeys; unpublished observations). Because the principal measure of stimulus control in these experiments was a decrease in responding, and 0.03 mg/kg ALPZ had no direct effects on responding (Experiment 1a), this dose was used to assess the stimulus effects of ALPZ. The assessment of stimulus effects of larger doses with direct rate-decreasing effects, either as a training dose or during generalization tests, would be more difficult in this paradigm because a rate-decreasing effect would confound the measure of discrimination. Pronounced rate-decreasing effects of drugs in other drug-discrimination paradigms have also been described as undesirable (Colpaert, 1987), presumably because they could interfere with stimulus control.

Rate-decreasing effects were not apparent at the beginning of drug-discrimination training, confirming the lack of direct effect of 0.03 mg/kg ALPZ. With several ALPZ/LiCl pairings, a significant decrease in the response rate occurred, suggesting that postsession LiCl was effective in suppressing responding. However, the decrease in baseline performance suggested that the rate-decreasing effects of LiCl were either not specifically associated with ALPZ or that there was some induction of the suppressive effects of ALPZ/LiCl pairings to subsequent saline/saline sessions. The change in responding in sessions following ALPZ/LiCl sessions seemed to substantiate the latter conclusion, because the extent of the suppression diminished as a function of the days since the last LiCl treatment.

Although the basis for the failure to establish discriminative control by ALPZ was not identified, the lack of direct effect of 0.03 mg/kg ALPZ suggested one possibility: This dose may have been too low to obtain control. This possibility was addressed in Experiment 2.

Table 1

Baseline rates of responding (*SD*) for each monkey, in the order of the various experimental conditions to which it was exposed. For Experiment 1, baseline is the mean of Thursdays during the dose-effect determinations. For Experiments 1b and 2, baseline is the mean of 4 to 6 days immediately preceding the start of conditioning procedures.

	Experiment		
	1a	1b	2
Monkey	ALPZ dose effect	ALPZ/LiCl	ALPZ/*d*-A
512	2.639 (0.245)	1.97 (0.162)	2.72 (0.272)
72	1.727 (0.408)	2.63 (0.219)	2.66 (0.237)
8221	1.840 (0.254)		
59	2.148 (0.385)		
2R	—	—	3.930 (0.120)
G91	—	—	2.458 (0.130)

EXPERIMENT 2

Because evidence of drug discrimination in Experiment 1 was weak (i.e., response rates during ALPZ/LiCl and saline/saline sessions were not clearly different), a higher presession dose of ALPZ was studied in Experiment 2. Because the overall degree of suppression produced by postsession LiCl in Experiment 1 was low, and previous studies (Glowa & Barrett, 1983) had shown postsession *d*-amphetamine (*d*-A) to be effective in suppressing responding under similar conditions, postsession *d*-A was used in Experiment 2.

METHOD

Subjects

Four male adult rhesus monkeys (*Macaca mulatta*), weighing approximately 8 to 9 kg, served as subjects. Monkeys 512 and 72 had previously participated in Experiment 1. The other 2 monkeys (2R and G91) had not been exposed previously to the drug-discrimination procedure. Between experimental sessions, subjects were housed individually and had continuous access to water. Weights were maintained at 85% of ad libitum weights by restricting access to food (Purina Monkey Chow) in the home cages.

Procedure

Responding was maintained under the same conditions as those described for Experiment 1a. On certain days, an injection of 0.1 mg/kg ALPZ was given in the home cage, the monkeys were seated in the chamber 60 min later, and the session was started. At the end of these sessions, the monkeys were given an injection of 1 mg/kg *d*-A and were left in the chamber for 15 min (ALPZ/*d*-A). On other

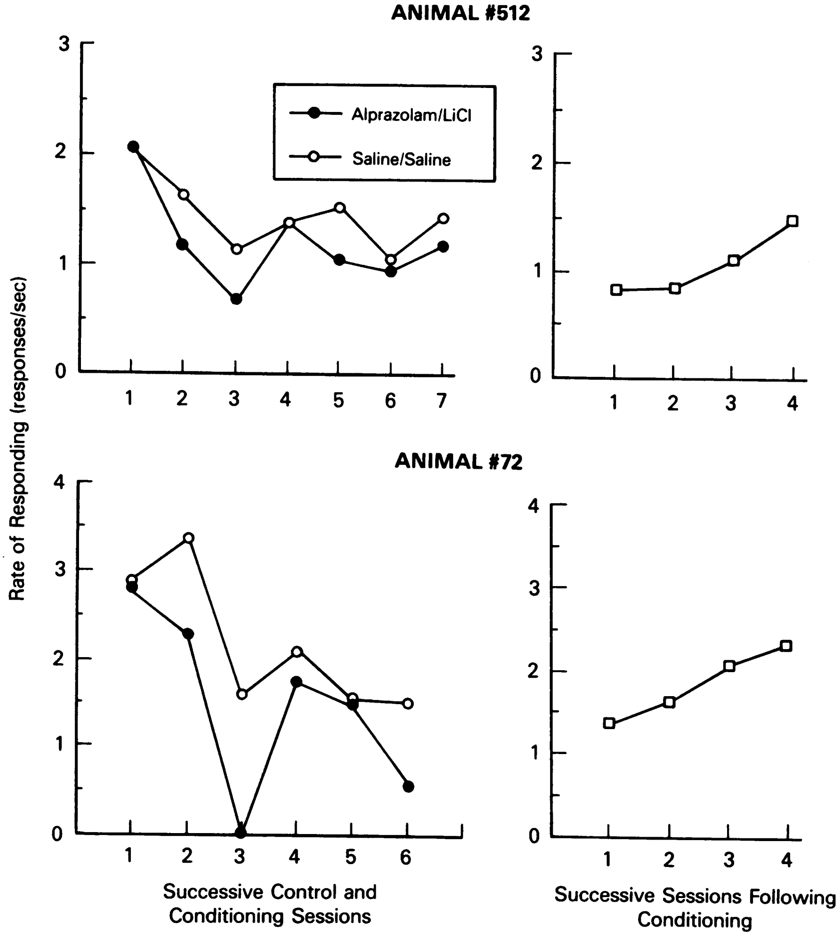

Fig. 2. Left panels: effects of alprazolam/lithium pairings (closed circles) and saline/saline pairings from the preceding day (open circles) on responding maintained by FR 30 food presentation in rhesus monkeys. Each point on the horizontal axis represents a successive pair of treatments (i.e., the first saline/saline and the alprazolam/lithium session to follow through the seventh saline/saline and lithium/alprazolam session to follow). Alprazolam (0.03 mg/kg, i.m.) was given 60 min before sessions that were concluded with an immediate postsession administration of 1.8 mEq/kg lithium chloride; saline was given in a similar manner both before and after the session. Right panels: the change in responding over intervening saline/saline sessions to follow a conditioning (alprazolam/lithium) session. Because the criterion for initiating a conditioning day was that rates of responding on the preceding saline/saline day were at least 1.0 response per second, a variable number (three to six) of sessions could occur between conditioning days.

days, the monkeys were given pre- and postsession injections of saline (saline/saline) in a similar manner. Experiments were typically conducted 5 days per week. ALPZ/*d*-A sessions usually occurred on Tuesdays and Fridays, with saline/saline sessions occurring on other days of the week. The effects during ALPZ/*d*-A sessions were measured for 10 pairings. An extinction phase, in which ALPZ was given before the session and saline was given after the session, was then studied for four ALPZ sessions.

Drugs

The procedures for ALPZ administration were the same as those described in Experiment 1, except the dose was 0.1 mg/kg. *d*-Amphetamine (Sigma) was dissolved in saline and injected i.m. in the thigh in a volume of 0.1 mL/kg body weight.

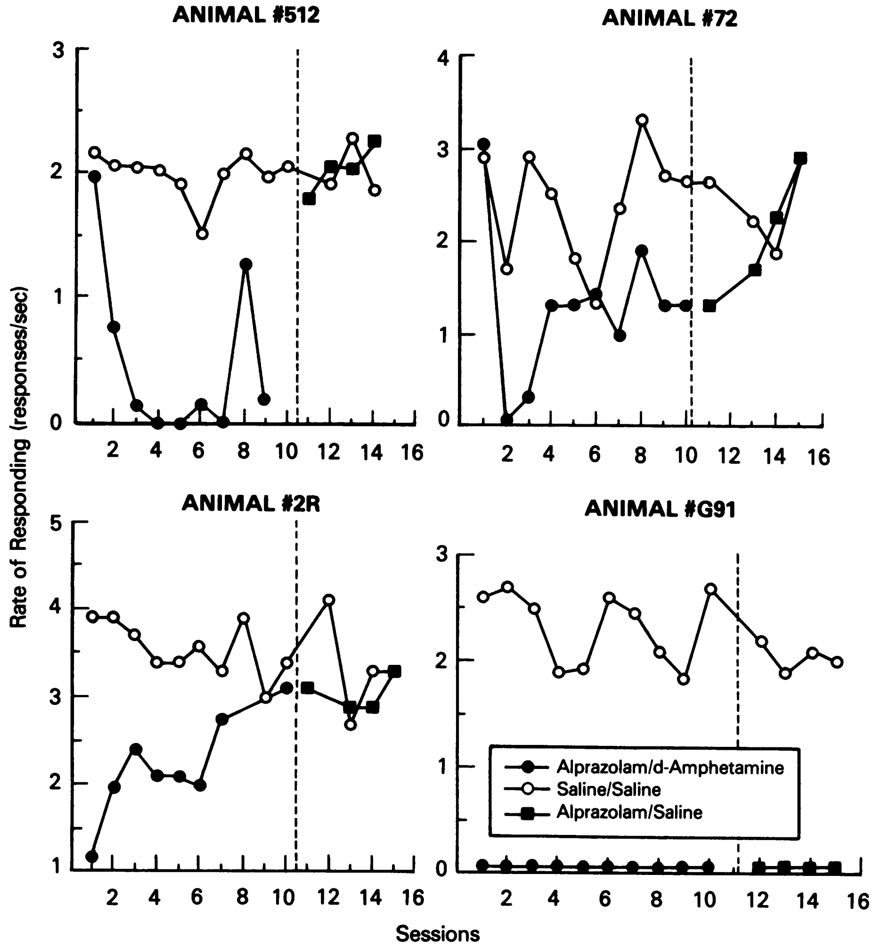

Fig. 3. Effects of alprazolam/*d*-amphetamine postsession pairing and saline given before and after sessions as a function of successive treatments for Monkeys 72, 512, 2R, and G91. Details are the same as in Figure 2.

Results

Baseline Performances

Rates and patterns of responding were similar to those seen in Experiment 1. Experimental conditions and control rates of responding are presented in Table 1.

Drug-Discrimination Assessment

Figure 3 shows that when ALPZ preceded sessions that were followed by *d*-A (ALPZ/*d*-A), responding generally decreased over subsequent ALPZ/*d*-A sessions. This effect was slightly different for each monkey. Responding dramatically decreased over the first several ALPZ/*d*-A sessions for Monkey 512 and Monkey 72; by the third session, responding had decreased to 8% and 10% of control for Monkey 512 and Monkey 72, respectively. Responding remained decreased (with the exception of Session 8) over the course of ALPZ/*d*-A sessions for Monkey 512, but recovered somewhat for Monkey 72. Responding was eliminated completely during the initial ALPZ/*d*-A session for Monkey G91 and Monkey 2R. For Monkey G91, responding remained low for all subsequent ALPZ/*d*-A sessions. In contrast, the rate-decreasing effects seen during ALPZ/*d*-A sessions diminished in Monkey 2R, with rates eventually approaching baseline levels. For all monkeys, rates of responding during saline/saline sessions generally remained at baseline levels, and, with the exception of the sixth saline/saline

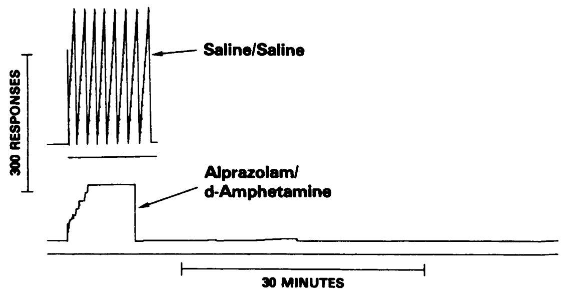

Fig. 4. Cumulative response recordings for Monkey 72 illustrating the effects obtained on the third alprazolam/*d*-amphetamine conditioning day (bottom) compared to the preceding saline/saline day (top). The pen pipped with each food presentation and reset after each lapse of 10 FR components.

session for Monkey 72, were always higher than rates during ALPZ/*d*-A sessions. During extinction sessions (i.e., ALPZ/saline; Figure 3, closed squares), rates of responding gradually increased to levels indistinguishable from baseline sessions (except for G91).

Figure 4 illustrates the magnitude of effect produced by ALPZ/*d*-A pairings. Responding during the third ALPZ/*d*-A session is compared with that occurring during the preceding saline/saline session for Monkey 72. After the completion of three ratio requirements, rates of responding abruptly decreased for more than 70 min.

Discussion

Responding decreased over ALPZ/*d*-A sessions in 2 of the 4 monkeys (512 and 72). This clearly indicates that ALPZ can serve as a conditional stimulus for response suppression associated with postsession drug administration. In Monkeys G91 and 2R, the effects were less interpretable. The immediate and complete suppression of responding obtained with G91, and possibly the initial suppression with Monkey 2R, which appeared to be a direct effect of ALPZ, precluded an assessment of the acquisition of drug discrimination. This suggests that, despite the rather uniform dose–effect functions obtained for the 4 monkeys in Experiment 1, individual differences in response to ALPZ can occur. Some of these differences may be related to prior exposure to ALPZ, because tolerance to its effects was demonstrated in Experiment 1. The monkeys in which clear effects were found (Monkey 512 and Monkey 72) had considerable experience with ALPZ before the ALPZ/*d*-A drug-discrimination assessment, and clear evidence for stimulus control was not obtained in the ALPZ-naive monkeys (Monkey 2R and Monkey G91).

Although Monkey 512 and Monkey 72 exhibited clear evidence of discriminative control by ALPZ, responding following several pairings was not completely suppressed. The moderate suppression may have been a function of the specific dose of *d*-A used. For both operant (Glowa & Barrett, 1983) and consummatory (Nathan & Vogel, 1975) responding, complete dose–effect data suggest that sufficiently large postsession doses are required to produce complete response suppression. Because relatively little data are available on the effects of different postsession doses of *d*-A in rhesus monkeys, the possibility that greater suppression may have been obtained if slightly higher doses of *d*-A were used remains plausible.

GENERAL DISCUSSION

The current studies extend previous demonstrations of the ability of postsession drug administration to suppress food-maintained operant responding in rats (Stolerman & D'Mello, 1978), pigeons (Glowa & Barrett, 1983), and squirrel monkeys (Bergman & Glowa, 1986) to the rhesus monkey. These experiments also extend previous studies that have shown that drug discrimination can be rapidly obtained using the conditioned taste-aversion design in rats (Kautz et al., 1989; Lucki, 1988; Mastropaolo et al., 1989; Riley et al., 1989) to the monkey. The demonstration of the rapid development of drug discrimination in the monkey using a conditioned taste-aversion paradigm suggests that these methods may have several advantages over more traditional drug-discrimination designs in which drug-appropriate responding is maintained by the delivery of a positive reinforcer.

The ability to develop drug discrimination rapidly is clearly of interest because traditional drug-discrimination techniques may require months of training before discriminative criteria are met (Overton, 1987). The rapid rate of development of response suppression (the primary measure of drug discrimination) in the present experiments was similar to that seen in earlier studies using nondrug stimuli (i.e., tastes) associated with postsession drug administration (Riley & Tuck, 1985; Stolerman & D'Mello, 1978). The degree of suppression can be quite dramatic (Figure 4). The differences obtained between different monkeys in the present experiments suggest that there may be specific behavioral determinants of these effects (prior exposure to drug stimuli, for example) that may enhance or diminish the likelihood of obtaining good behavioral control with drug stimuli (Barrett & Olmstead, 1989).

Another potential advantage of the present method is the continuous nature of the effect produced. In conventional procedures, data collection is often restricted to the first few reinforcers, because delivery of the reinforcing event sets the occasion for responding. The primary measure is the proportion of subjects respondings on the drug-appropriate manipulandum. This often results in quantal-like data, in which all of the initial responding occurs on a single manipulandum. The use of a post-session event allows incorporation of entire-session rates of responding in the assessment of stimulus control. The use of ratio schedules also contributes to the magnitude of the effect obtained, because high rates are sensitive to the suppressant effects of drugs (McMillan, 1975).

Another possible advantage of the present method is that it is sensitive. Very low doses of ALPZ, as determined by their marginal effects on FR responding, were effective discriminative stimuli. Conventional drug-discrimination procedures often use high training doses that may have unconditioned effects on performance (Overton, 1987; see also Monkeys 2R and G91 in Experiment 2). The ability of low doses of ALPZ to maintain stimulus control, while tolerance occurred to its rate-decreasing effects, further suggests the conditioned taste-aversion paradigm may be a particularly sensitive procedure to assess the stimulus effects of drugs. However, the attenuation of effects seen in Monkeys 2R and 72 in Experiment 2a may represent the development of tolerance to the stimulus effects of ALPZ. Although tolerance typically does not appear to play a role in the discriminative effects of similar agents (Ator & Griffiths, 1989; York & Winter, 1975), further studies should assess this possibility.

ALPZ is a triazolo 1,4-benzodiazepine that is widely prescribed as an anxiolytic agent (Dawson, Jue, & Brogden, 1984). Previous studies have demonstrated that drugs with anxiolytic actions can increase suppressed responding (Geller, Kulak, & Seifter, 1962), and little tolerance to this effect occurs (McMillan, 1975). Studies using conditioned taste-aversion designs to suppress drinking (Riley & Lovely, 1978) or operant responding (Bergman & Glowa, 1986; Glowa & Barrett, 1983) have also found that drugs with anxiolytic actions can attenuate response suppression. This effect might be expected to prevent the development of response suppression. In the present studies, however, response suppression developed in the presence of ALPZ. This suggests that alprazolam lacks the ability to increase suppressed responding under some circumstances (Wettstein, 1990). On the other hand, the attenuation of the response suppression that developed in Experiment 2 may have been due to the rate-increasing effects of ALPZ. Further studies designed to assess the discriminative properties of drugs without rate-increasing effects on suppressed responding may resolve this issue.

In conclusion, the present studies demonstrate that presession administration of a relatively low dose of ALPZ (as assessed by its lack of direct effect) can be an effective discriminative stimulus, because responding in its presence was selectively suppressed by post-session administration of *d*-A. The use of operant responding within the taste-aversion paradigm provided a quantitative measure of drug discrimination that compares favorably to results obtained with traditional drug-discrimination designs. Most importantly, the acquisition of the discrimination was rapid. The ability of ALPZ to set the occasion for response suppression differed across individuals, and these differences may have depended upon features such as individual sensitivity or prior exposure to ALPZ. The further use of the within-subject design should allow a more detailed analysis of the role of drug history in such effects and provide direct comparisons of the rates of development of discrimination in this paradigm and more conventional procedures. Because the current results suggest that prior exposure to the procedure may enhance the development of discrimination, balanced designs should be used. Nevertheless, the present results strongly encourage the further development of the conditioned aversion paradigm to assess the discriminative effects of drugs.

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